



P21480.A16

Application No. 09/926,218

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Arne HOLMGREN et al.

Group Art Unit : 1621

Appl. No : 09/926,218
(National Stage of PCT/JP00/02076)

Examiner : Kumar

I.A. Filed : March 31, 2000

For : SUBSTRATE FOR THIOREDOXIN REDUCTASE

APPEAL BRIEF UNDER 37 C.F.R. 1.192

Commissioner for Patents
U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, Mail Stop _____
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir :

This Appeal is from the Examiner's Final Rejection of claims 13-25 as set forth in the Final Office Action mailed from the U.S. Patent and Trademark Office on December 23, 2003.

A Notice of Appeal to the December 23, 2003 Final Office Action was filed June 1, 2004 accompanied by a Request for Extension of Time for two months, whereby the initial due date for filing of the Appeal Brief is set to expire two months thereafter, or August 2, 2004 (August 1, 2004 being a Sunday). Appellant therefore requests an extension of time for one month to extend the time for filing the Appeal Brief until September 1, 2004. The extension of time fee and the requisite fee under 37 C.F.R. 1.17(s) in the amount of \$330.00 for filing this Appeal Brief is being paid by check, enclosed herewith.

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Authorization is hereby provided to charge any fee necessary for maintaining the pendency of this application, including any appeal fee and any extension of time fee that may be necessary, to Deposit Account No. 19-0089.

This Appeal Brief is being submitted in triplicate.



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1. REAL PARTY IN INTEREST

The real party in interest is Daiichi Pharmaceuticals Co., Ltd. Of Tokyo, Japan by an assignment which was recorded on January 28, 2002, at Reel 012522, Frame 0295.

2. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the decision of the Board of Patent Appeals and Interferences in the pending appeal.

3. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 1-12 are canceled, and claims 13-25 are pending in this application.

Of the pending claims, claims 13-25 have been finally rejected in the Final Office Action.

The claims that are under appeal, i.e., claims 13-25, are reproduced in the APPENDIX attached hereto.

4. STATUS OF AMENDMENTS FILED SUBSEQUENT TO FINAL REJECTION

Appellant filed an Amendment Under 37 C.F.R. 1.116 on April 28, 2004. In the Amendment, claims 15, 17-19 and 24 were amended.

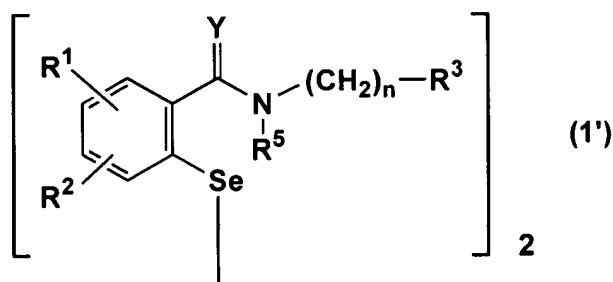
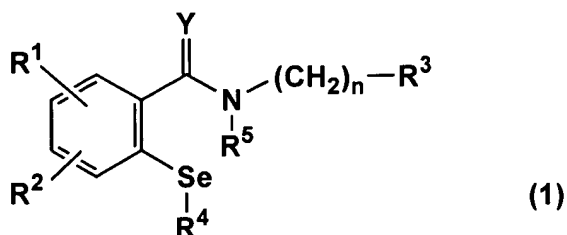
An Advisory Action was mailed May 25, 2004 indicating that Appellant's Amendment filed April 28, 2004 will be entered for purposes of appeal, whereby the claims under appeal are the claims as presented in the Amendment Under 37 C.F.R. 1.116, filed April 28, 2004.

5. SUMMARY OF INVENTION

As disclosed in the specification, at page 1, beginning in the Disclosure of the Invention, an object of the present invention is to provide substances which function as a substrate for thioredoxin reductase and can activate the thioredoxin/thioredoxin reductase system. In particular, the object is to provide a substance which can enhance peroxidase activity proceeded by thioredoxin reductase. As discussed in the specification in the following paragraph, the inventors of the present invention conducted intensive studies and found that selenium compounds such as 2-phenyl-1,2-benzisoselenazol-3(2H)-one can function as substances of thioredoxin reductase by repeated self reduction-oxidation similarly to thioredoxin in the thioredoxin/thioredoxin reductase system, and that the compounds can remarkably enhance peroxidase activity of thioredoxin reductase in the presence of thioredoxin reductase and thioredoxin.

Appellant's invention is able to achieve a variety of beneficial results using the substrate for thioredoxin reductase of the present invention which activates the thioredoxin/thioredoxin reductase system. For example, as disclosed in the specification such as beginning at page 3, first full paragraph, and in the disclosure beginning on page 12 under the heading "Reduction of compound A by human thioredoxin reductase" and as recited in claim 13, the present invention provides a method

for reduction of a substrate with thioredoxin reductase, comprising combining the thioredoxin reductase, the substrate and NADPH under conditions to reduce the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S-

glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R⁵ represents a hydrogen atom or a C₁-C₆ alkyl group, or R⁴ and R⁵ may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized. Moreover, as recited in claim 14, the substrate can comprise a substance selected from the group consisting of 2-phenyl-1,2-benziso-selenazol-3(2H)-one or a ring-opened form thereof and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Moreover, as disclosed in the specification, page 3, beginning in the second full paragraph, the present invention provides a method of enhancing peroxidase activity of thioredoxin reductase, comprising combining NADPH, thioredoxin reductase, thioredoxin and a substrate under conditions to enhance peroxidase activity of thioredoxin reductase, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, as defined in independent claim 17, the present invention provides a method of oxidizing reduced thioredoxin by a substrate, the method comprising combining reduced thioredoxin and a substrate under conditions to oxidize the reduced thioredoxin with the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the first full paragraph.

Still further, as recited in independent claim 18, the present inventions provides a method for reducing a peroxide comprising combining thioredoxin, thioredoxin reductase, NADPH and a

substrate under conditions to reduce the peroxide, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the first full paragraph.

Still further, as recited in independent claim 19, the present invention provides a method of preventing peroxidation of a substance comprising combining thioredoxin, thioredoxin reductase and NADPH with a substrate under conditions to prevent peroxidation of the substance, the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the first full paragraph.

Still further, as recited in independent claim 20 and as further defined in dependent claim 20, the present invention provides a method for enhancing peroxidase activity of thioredoxin reductase in vivo which comprises administering a peroxidase activity enhancing effective amount of a substrate to a mammal (such as a human), the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the second full paragraph.

Still further, as recited in independent claim 22 and dependent claim 23, the present invention provides a method of reducing a peroxide in vivo which comprises administering an peroxide reducing effective amount of a substrate to a mammal (such as a human), the substrate comprising a substance selected from the group consisting of a compound represented by the following general

formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the second full paragraph.

Still further, as recited independent claim 24 and dependent claim 25, the present invention provides a method of preventing peroxidation of a substance in vivo by oxidizing reduced thioredoxin in a peroxidase reaction proceeded by thioredoxin reductase comprising administering a peroxidation preventing effective amount of a substrate to a mammal (such as a human), the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof, such as disclosed in the specification at page 8, the second full paragraph.

6. CONCISE STATEMENT OF ISSUES

(a) Whether claims 13-25 are properly rejectable under 35 U.S.C. 102(b) as being anticipated by Arteel et al. (hereinafter "Arteel"), Chem. Res. Toxic., Vol. 12, 1999, pages 264-269.

(b) Whether claims 13-25 are properly rejectable under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Arteel and Muller et al. (hereinafter "Muller"), Biochemical Pharmacology, Vol. 33, No. 20, pages 3235-3239, 1984.

7. GROUPING OF CLAIMS

For each ground of rejection included in the Examiner's Final Rejection that applies to more than one claim, the rejected claims do not stand or fall together for the reasons given below.

8. ARGUMENTS

(a) Claims 13-25 are not properly rejectable under 35 U.S.C. 102(b) as being anticipated by Arteel, Chem. Res. Toxic., Vol. 12, 1999, pages 264-269.

In this ground of rejection, it is asserted in the Final Office Action that:

As explained in paper #8, Arteel et al teach every element of instant claims. For example, see line 1 of the abstract wherein mammal is referenced, column 1, 2nd paragraph lines 1-3, and lines 7-8, 1st paragraph, column 2, describe the elements of the claims.

Moreover, in the Advisory Action, the Examiner asserts that:

Claims 13-25 stand rejected as anticipated under 35 USC102(b) over Arteel and obvious under 35 USC 103 over combined teachings [sic] of Arteel and Muller et al for the reasons of record as set forth dated 12/31/03 and 3/10/03, It is clear that ebselene is a substrate for the thioredoxin reductase, and the function of reductase to reduce the substrate.

In contrast to the assertions in the Final Office Action and the erroneous indication in the Advisory Action, Appellant respectfully submits that Arteel does not teach each and every element recited in Appellant's claims whereby the anticipation rejection is without appropriate basis and should be withdrawn.

Appellant notes that Arteel is directed to a study involving materials that are similar to those used in Appellant's processes. Therefore, the anticipation rejection appears to be asserting that because similar materials are included in Arteel's study, the function of the materials in

Arteel's study would be the same as recited in Appellant's claims. However, in contrast to the assertions in the rejections, Arteel does not teach each any every element recited in Appellant's claimed invention.

In contrast to the assertions in the rejection, Arteel does not teach any methods wherein ebselen is used as a substrate for thioredoxin reductase. Arteel performs experiments with respect to the activity of mammalian thioredoxin reductase using a peroxynitrite reductase. Thus, at page 264, at the bottom of the left-hand column, Arteel discloses, "Here we investigated whether mammalian TR [thioredoxin reductase] can function as a peroxynitrite reductase." In performing the study, as disclosed in the Results section at page 265, left-hand column, Arteel infuses peroxynitrite to maintain a 0.2 μ M steady-state concentration in potassium phosphate buffer. Arteel uses benzoate hydroxylation and nitrite formation as indices of oxidation reactions of peroxynitrite and of peroxynitrite reduction. Arteel particularly notes that when selenocystine or ebselen are present in the reaction mixture, there is a significant suppression of benzoate hydroxylation and an increase in nitrite formation until the NADPH was oxidized. **Arteel particularly specifies that the addition of thioredoxin did not enhance these effects** (page 264, in the Abstract). Moreover, on page 265, right-hand column, Arteel discloses that. "Addition of TR to ebselen had no effect under these conditions (▼)."

Therefore, Arteel should be considered to be nonenabling for processes wherein thioredoxin is present as Arteel does not teach or suggest any need for having the thioredoxin present in the reaction.

Still further, Arteel discusses the formation of ebselen selenoxide by oxidation of ebselen

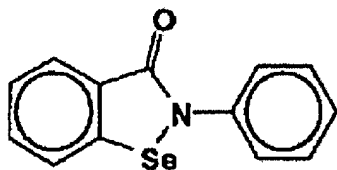
by bolus addition of peroxyxynitrite. For example, attention is directed to Arteel, page 265 under the heading "Formation of Ebselen Selenoxide and Reduction by TR" and page 267 under the heading "Reduction of Ebselen Selenoxide by TR".

Thus, Appellant notes that it is apparent that Arteel is directed to the investigation of the activity of mammalian thioredoxin reductase as a peroxyxynitrite reductase. Appellant does note that Arteel performs experiments with ebselen, such as disclosed at page 265, right-hand column. Moreover, Arteel discusses, at page 268, the right-hand column, an affinity of ebselen for thioredoxin reductase, and the role of thioredoxin in the thioredoxin reductase-albumin complex. However, Appellant directs attention to Engman et al., "Diaryl chalcogenides as selective inhibitors of thioredoxin reductase and potential antitumor agents", Anticancer Res. 1997 Nov-Dec;17(6D):4599-605. From a review of this document, it can be seen that Engman as well as **Arteel do not disclose the use of ebselen as a substrate for thioredoxin reductase. Instead, Arteel pertains to ebselen selenoxide created by incubation with peroxyxynitrite.**

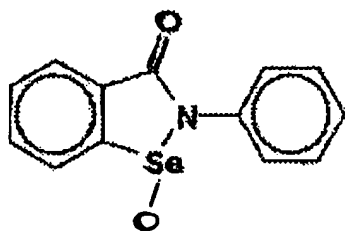
Expanding on the above, Appellant notes that in its results and discussion, at page 268, right column, at the top of the column, Arteel cites Engman (Reference No. 22) for its disclosure of **ebselen being an inhibitor of thioredoxin reductase**, and discusses a mechanism that is not in conformance with that of the presently disclosed and claimed invention. Furthermore, Arteel does not teach or suggest any effect of thioredoxin reductase with ebselen. Therefore, this prior art, as stated in Engman merely discloses, "The organoselenium compound Ebselen was found to be a competitive inhibitor of human thioredoxin reductase (K_i 2.8 microM), while a number of organotellurium compounds were found to be noncompetitive inhibitors (K_is 2.3 to 35.2

microM).” Thus, the prior art at most teaches that ebselen is an inhibitor of thioredoxin reductase, and that ebselen selenoxide can be a substrate. However, Appellants’ claims do not include ebselen selenoxide.

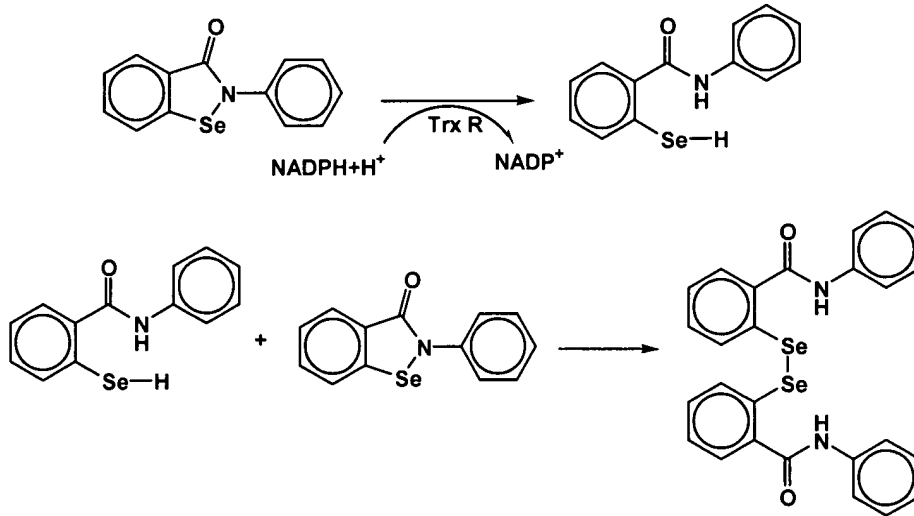
To assist a further understanding of Appellant’s invention, Appellant notes that ebselen has the following formula:



Ebselen selenoxide has the following formula:



Moreover, the reaction of ebselen in Appellant’s system does not form ebselen selenoxide, the compound disclosed in Arteel, but produces compounds according to the following reaction scheme, as disclosed on pages 13 and 14 of Appellant’s specification.



Therefore, summarizing the above, Arteel discloses that:

- (1) Ebselen inhibits thioredoxin reductase, and it is therefore expected that addition of ebselen would shut off effects of thioredoxin reductase.
- (2) The strong oxidant peroxyxynitrite is reduced by thioredoxin reductase provided that ebselen is present. The mechanism being that ebselen is oxidized to ebselen selenoxide which is reduced by thioredoxin reductase.
- (3) There is no effect by adding thioredoxin.

In contrast, according to Appellant's invention and included in Appellant's claims, the substrate, such as ebselen, is a substrate for the thioredoxin reductase, not an inhibitor. As part of Appellant's invention, a fast reaction of thioredoxin reductase directly with ebselen to the selenol which is reoxidized removing peroxides is utilized. Ebselen provides a fast reaction of reduced thioredoxin. That is ebselen itself is also a direct substrate for thioredoxin. The addition of ebselen will therefore oxidize thioredoxin which explains its anti-inflammatory

effects. For example, **thioredoxin oxidation as recited in Appellant's claims is not taught or suggested in any prior art of record.**

Appellant respectfully submits that **a substance which is an inhibitor of an enzyme is not a substrate unless it is a suicide substrate, which kills the enzyme by covalent modification.** For example, the Abstract in Arteel merely states in the last sentence that, "In parallel experiments, thioredoxin reductase efficiently reduced ebselen selenoxide back to ebselen". Moreover, in the above-noted portion of page 268 of Arteel, it is stated that, "Ebselen has been shown previously to have an affinity for TR, competitively inhibiting the Trx-dependent reduction of insulin by TR with an apparent K_i of 2.8 μM (22)." **Arteel shows no effect of thioredoxin on reduction of ebselen selenoxide by NADPH and thioredoxin reductase.**

From the above, it is apparent that Arteel does not teach the invention as disclosed and claimed by Appellant. Thus, amongst other deficiencies in the prior art of record, the prior art does not teach or suggest that ebselen is an outstanding substrate for reduced thioredoxin. This is not taught or suggested in the prior art of record and, without wishing to be bound by theory, is an important manner in which ebselen hinders inflammation by preventing thioredoxin from reducing and activating a range of transcription factors, including NF κ B. **Thus, according to the present invention, ebselen can target both thioredoxin reductase and thioredoxin with separate results.**

Moreover, as noted above, prior to Appellant's invention, one having ordinary skill in the art would be under the belief that ebselen is an inhibitor of thioredoxin reductase, and not a substrate according to the processes disclosed and claimed by Appellant's.

In contrast to the prior art of record, the present invention recognizes and demonstrates that ebselen is a substrate being reduced by NADPH and thioredoxin reductase with a low K_m -value meaning that it is a very good substrate undergoing unlimited cycles of oxidation/reduction in the presence of hydrogen peroxide without affecting the activity of the enzyme. The reduced ebselen is called ebselen selenol and has the Se-N bond broken by reduction. The selenol is oxidized back to ebselen by hydrogen peroxide or another peroxide and a new cycle starts. The reaction is ultimately driven by NADPH. Reduced thioredoxin strongly enhances the thioredoxin reductase reaction which is also proven by determination of the rate of reduction of ebselen by reduced thioredoxin using kinetics with tryptophan fluorescence. The result, never seen before, is that ebselen is a very efficient oxidant of reduced thioredoxin.

Appellant notes that the Examiner's comments in the Final Office Action acknowledge Appellant's arguments, but assert that a concentration has not been claimed. In contrast to this assertion, Appellant are not arguing concentrations, but are referring to reaction rates, and the unexpected fact reaction associated with Appellant's methods.

Moreover, the remarks in the Final Office Action disregard the negative teachings in Engman by asserting that, "The Engman reference has not been cited and is not required for supporting the instant rejection." However, the question is not whether the rejection is utilizing Engman for its support, but whether the rejection can be maintained in view of the negative teachings of Engman, which negative teachings also appear in Arteel. In other words, the rejection cannot ignore the disclosure of Engman, which disclosure is included in Arteel.

The Final Office Action also asserts that Appellant is not claiming the mechanism, but the function. However, Appellant is claiming the methods recited in the present claims, which methods are not disclosed in Arteel for the reasons set forth above.

The Examiner also contends that, "Applicants argue that in contrast to the reference, Ebselene is substrate in the instant claims being reduced by NADPH and thioredoxin reductase. Arteel teaches the same thing." Certainly, for the reasons set forth above, Appellant's methods as recited in Appellant's claims are not anticipated by Arteel. Arteel merely discloses certain of Appellant's claimed elements, but not the methods recited in Appellant's claims.

Being more specific to the pending claims, Applicants respectfully submit that Arteel does not teach, as recited in Appellant's independent claim 13, a method for reduction of a substrate with thioredoxin reductase, comprising combining the thioredoxin reductase, the substrate and NADPH under conditions to reduce the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof. For example, Arteel does not teach Appellant's method let alone such a method including substrates as disclosed and claimed by Appellant. As noted above, Arteel discloses ebselen oxide in the reaction which is not included in Appellant's substrates. Dependent claim 14 further patentably defines that the substrate comprises a substance selected from the group consisting of 2-phenyl-1,2-benziselenazol-3(2H)-one or a ring-opened form thereof and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, Appellant respectfully submits that Arteel does not teach, as recited in Appellant's independent claim 15, a method of enhancing peroxidase activity of thioredoxin reductase, comprising combining NADPH, thioredoxin reductase, thioredoxin and a substrate under conditions to enhance peroxidase activity of thioredoxin reductase, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof. Dependent claim 16 further patentably defines that the substrate comprises a substance selected from the group consisting of 2-phenyl-1,2-benzisoselenazol-3(2H)-one or a ring-opened form thereof and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, Appellant respectfully submits that Arteel does not teach, as recited in Appellant's independent claim 17, a method of oxidizing reduced thioredoxin by a substrate, the method comprising combining reduced thioredoxin and a substrate under conditions to oxidize the reduced thioredoxin with the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, Appellant respectfully submits that Arteel does not teach, as recited in Appellant's independent claim 18, a method for reducing a peroxide comprising combining thioredoxin, thioredoxin reductase, NADPH and a substrate under conditions to reduce the peroxide, the substrate comprising a substance selected from the group consisting of a compound represented

by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, Appellant respectfully submits that Arteel does not teach or suggest, as recited in Appellant's independent claim 19, a method of preventing peroxidation of a substance comprising combining thioredoxin, thioredoxin reductase and NADPH with a substrate under conditions to prevent peroxidation of the substance, the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

Still further, Appellant respectfully submits that Arteel does not teach or suggest, as recited in Appellant's independent claim 20, a method for enhancing peroxidase activity of thioredoxin reductase in vivo which comprises administering a peroxidase activity enhancing effective amount of a substrate to a mammal, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof. Dependent claim 21 further patentably defines that the mammal is a human.

Still further, Appellant respectfully submits that Arteel does not teach or suggest, as recited in Appellant's independent claim 22, a method of reducing a peroxide in vivo which comprises administering an peroxide reducing effective amount of a substrate to a mammal, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate

thereof and a solvate thereof. Dependent claim 23 further patentably defines that the mammal is a human.

Still further, Appellant respectfully submits that Arteel does not teach or suggest, as recited in Appellant's independent claim 24, a method of preventing peroxidation of a substance in vivo by oxidizing reduced thioredoxin in a peroxidase reaction proceeded by thioredoxin reductase comprising administering a peroxidation preventing effective amount of a substrate to a mammal, the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof. Dependent claim 25 further patentably defines that the mammal is a human

Thus, Arteel does not teach Appellant's independent claims or any combination of the features of the independent claims with the dependent claims.

In view of the above, the assertions made in the rejection and the Advisory Action are without sufficient basis, whereby the anticipation rejection is improper, and should be reversed.

(b) Claims 13-25 are not properly rejectable under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Arteel and Muller

In the Final Office Action, it is asserted that:

As stated above, Arteel teaches every element of the instant claims. Muller et al further teach that Ebselene is an enhancer of the peroxidase activity (in fact Arteel teach this property inherently).

Appellant respectfully submits for the reasons set forth above that Arteel does not anticipate Appellant's invention. For the sake of brevity, Appellant is not repeating the arguments over Arteel, but incorporate them herein as if set forth in full.

Regarding the use of Muller, Appellant's specification discloses at page 2, lines 2-6, that Muller discloses that Appellant's compounds can reduce a peroxide (active oxygen) by glutathione peroxidase-like activity. However, the specification points out that the reduction of a peroxide by glutathione peroxidase is based on a totally different mechanism from that proceeded by thioredoxin reductase.

In particular, Muller is directed to the glutathione peroxidase-like activity of ebselen in vitro, in contrast to its sulfur analog, PZ25, and to its antioxidant activity. Muller discloses glutathione peroxidase and glutathione, and does not teach or suggest any relation of this activity to thioredoxin reductase activity, thioredoxin activity and/or thioredoxin/thioredoxin reductase activity.

Additionally, glutathione is a small peptide acting non-enzymatically, and therefore requires high concentrations. It is a different mechanism than the enzymatic system of the present invention.

Thus, Appellant respectfully submits that there is no motivation for using the disclosure of Muller to explain Arteel. Muller does not provide any motivation for providing substances which function as a substrate for thioredoxin reductase and can activate the thioredoxin/thioredoxin reductase system including providing a substance which can enhance peroxidase activity proceeded by thioredoxin reductase. As noted above, Muller discloses glutathione peroxidase and glutathione, and does not teach or suggest any relation of this activity to thioredoxin reductase activity, thioredoxin activity and/or thioredoxin/thioredoxin reductase activity. Moreover, even if for the sake of argument the disclosures were combined, the

presently claimed invention would not be present, especially because any combination of the documents would not teach or suggest Appellant's claimed methods which include use of compound such as ebselen as a substrate.

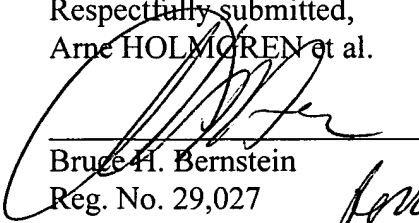
Thus, Muller does not make up for the deficiencies of Arteel, and each of Appellant's claims recites a patentable invention over any combination of Arteel and Muller.

In view of the above, the rejection should be withdrawn, and each of the claims should be indicated to be allowable over the prior art.

9. CONCLUSION

For the reasons set forth above, it is respectfully submitted that the Examiner has failed to establish either that Appellant's claims are anticipated by Arteel, or a prima facie case of obviousness, which is a prerequisite for maintaining a rejection under 35 U.S.C. 103(a). The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
Arne HOLMGREN et al.

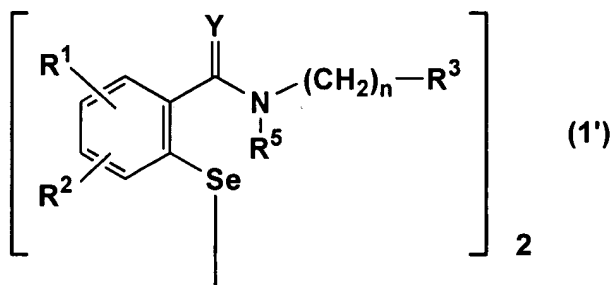
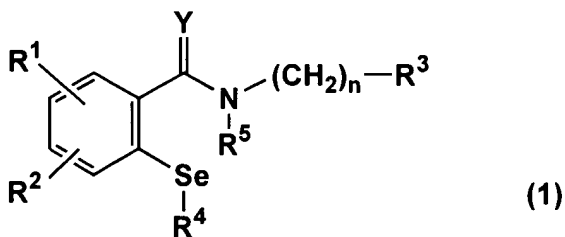

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Agreds. 33.08.04

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APPENDIX

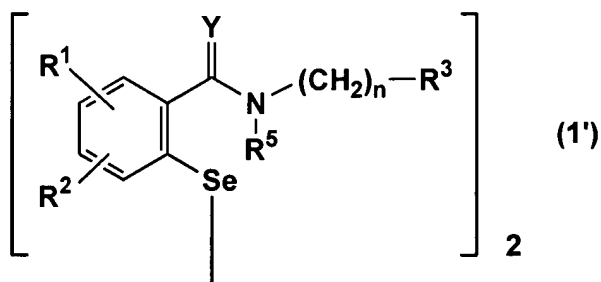
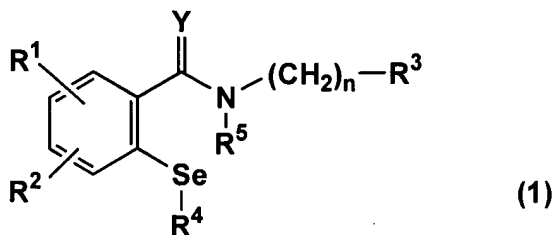
Claim 13. A method for reduction of a substrate with thioredoxin reductase, comprising combining the thioredoxin reductase, the substrate and NADPH under conditions to reduce the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R¹ and R² independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C₁-C₆ alkyl group, or a C₁-C₆ alkoxy group, or R¹ and R² may combine together to represent methylenedioxy group; R³ represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R⁴ represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α-amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R⁵ represents a hydrogen atom or a C₁-C₆ alkyl group, or R⁴ and R⁵ may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 14. The method according to claim 13 wherein the substrate comprises a substance selected from the group consisting of 2-phenyl-1,2-benziso-selenazol-3(2H)-one or a ring-opened form thereof and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

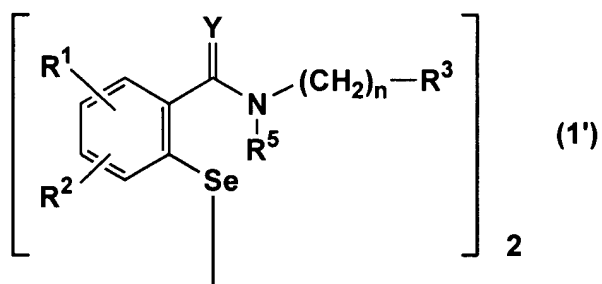
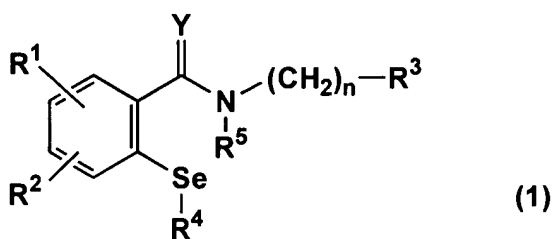
Claim 15. A method of enhancing peroxidase activity of thioredoxin reductase, comprising combining NADPH, thioredoxin reductase, thioredoxin and a substrate under conditions to enhance peroxidase activity of thioredoxin reductase, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R^5 represents a hydrogen atom or a C_1 - C_6 alkyl group, or R^4 and R^5 may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 16. The method according to claim 17 wherein the substrate comprises a substance selected from the group consisting of 2-phenyl-1,2-benzisoselenazol-3(2H)-one or a ring-opened form thereof and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof.

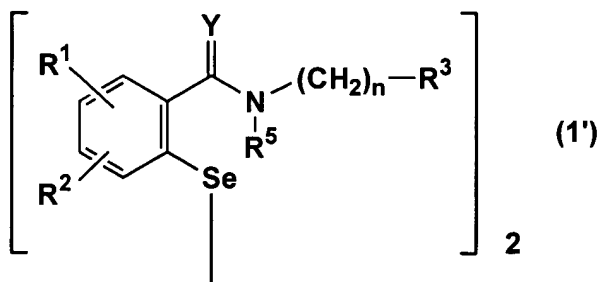
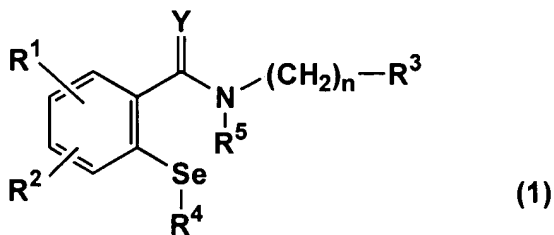
Claim 17. A method of oxidizing reduced thioredoxin by a substrate, the method comprising combining reduced thioredoxin and a substrate under conditions to oxidize the reduced thioredoxin with the substrate, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic

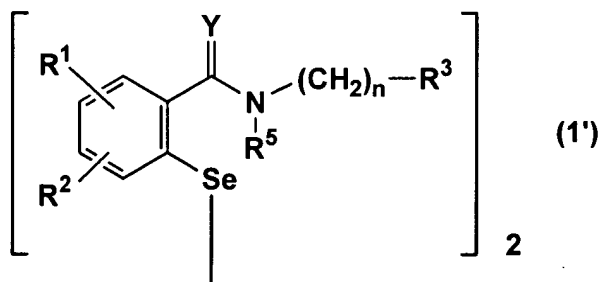
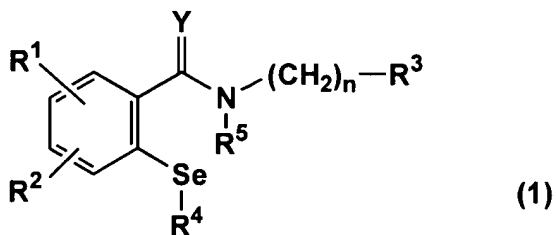
group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R^5 represents a hydrogen atom or a C_1 - C_6 alkyl group, or R^4 and R^5 may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 18. A method for reducing a peroxide comprising combining thioredoxin, thioredoxin reductase, NADPH and a substrate under conditions to reduce the peroxide, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R¹ and R² independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C₁-C₆ alkyl group, or a C₁-C₆ alkoxy group, or R¹ and R² may combine together to represent methylenedioxy group; R³ represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R⁴ represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R⁵ represents a hydrogen atom or a C₁-C₆ alkyl group, or R⁴ and R⁵ may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

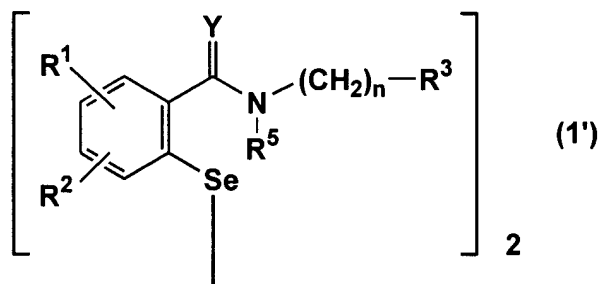
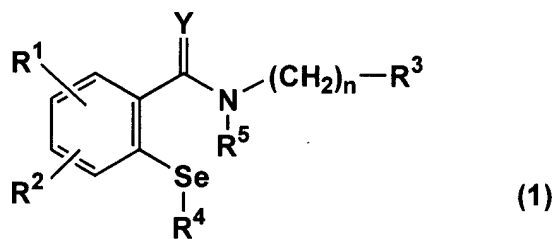
Claim 19. A method of preventing peroxidation of a substance comprising combining thioredoxin, thioredoxin reductase and NADPH with a substrate under conditions to prevent peroxidation of the substance, the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S- glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R^5 represents a hydrogen atom or a C_1 - C_6 alkyl group, or R^4 and R^5 may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 20. A method for enhancing peroxidase activity of thioredoxin reductase in vivo which comprises administering a peroxidase activity enhancing effective amount of a substrate to a

mammal, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:

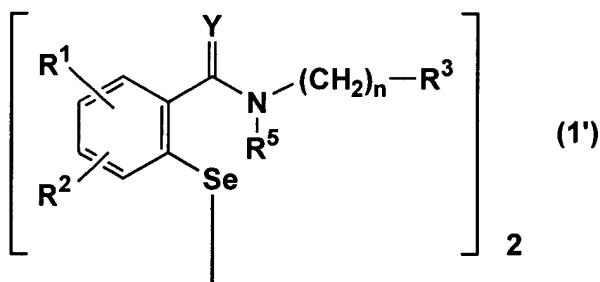
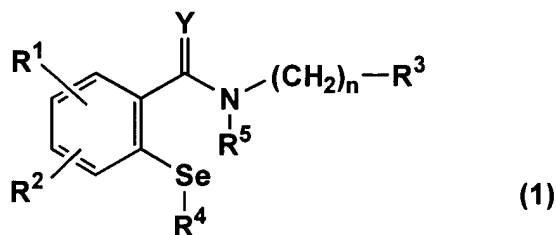


wherein R¹ and R² independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C₁-C₆ alkyl group, or a C₁-C₆ alkoxy group, or R¹ and R² may combine together to represent methylenedioxy group; R³ represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R⁴ represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R⁵ represents a hydrogen atom or a C₁-C₆ alkyl group, or R⁴ and R⁵ may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 21. The method according to claim 20 wherein the mammal is a human.

Claim 22. A method of reducing a peroxide in vivo which comprises administering an peroxide reducing effective amount of a substrate to a mammal, the substrate comprising a substance selected from the group consisting of a compound represented by the following general formula

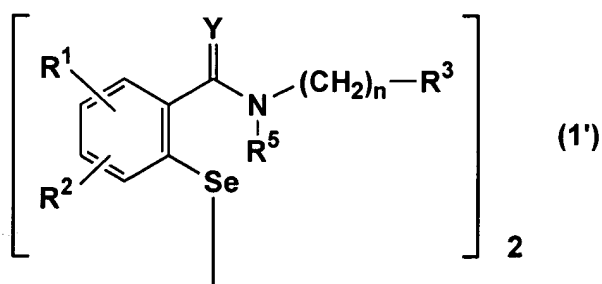
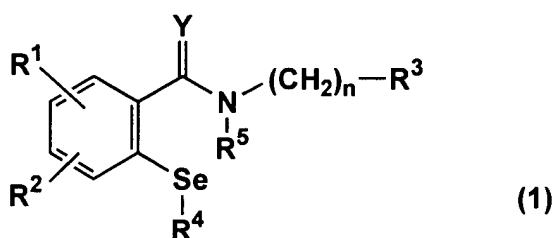
(1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S- glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R^5 represents a hydrogen atom or a C_1 - C_6 alkyl group, or R^4 and R^5 may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 23. The method according to claim 22 wherein the mammal is a human.

Claim 24. A method of preventing peroxidation of a substance in vivo by oxidizing reduced thioredoxin in a peroxidase reaction proceeded by thioredoxin reductase comprising administering a peroxidation preventing effective amount of a substrate to a mammal, the substrate being selected from the group consisting of a compound represented by the following general formula (1) or (1') and a physiologically acceptable salt thereof, and a hydrate thereof and a solvate thereof:



wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, a C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy group, or R^1 and R^2 may combine together to represent methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7-membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, and the aryl group, the aromatic heterocyclic group, the cycloalkyl group, and the cycloalkenyl group may be substituted with one or more substituents; R^4 represents a hydrogen atom, a hydroxyl group, a -S-glutathione group, a -S- α -amino acid group, or an aralkyl group whose aryl moiety may be substituted with one or more substituents; R^5 represents a hydrogen atom or a C_1 - C_6 alkyl group, or

R⁴ and R⁵ may combine together to represent single bond; Y represents oxygen atom or sulfur atom; n represents an integer of from 0 to 5; and the selenium atom may be oxidized.

Claim 25. The method according to claim 24 wherein the mammal is a human.